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Fluid challenges in intensive care: the FENICE study

A global inception cohort study

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Abstract *Background:* Fluid challenges (FCs) are one of the most commonly used therapies in critically ill patients and represent the corner-stone of hemodynamic management

in intensive care units. There are clear benefits and harms from fluid therapy. Limited data on the indication, type, amount and rate of an FC in critically ill patients exist in the literature. The primary aim was to evaluate how physicians conduct FCs in terms of type, volume, and rate of given fluid; the secondary aim was to evaluate variables used to trigger an FC and to compare the proportion of patients receiving further fluid administration based on the response to the FC. *Methods:* This was an observational study conducted in ICUs around the world. Each participating unit entered a maximum of 20 patients with one FC. *Results:* 2213 patients were enrolled and analyzed in the study. The median [interquartile range] amount of fluid given during an FC was 500 ml (500–1000). The median time was 24 min (40–60 min), and the median rate of FC was 1000 [500–1333] ml/h. The main indication for FC was hypotension in 1211 (59 %, CI 57–61 %). In 43 % (CI 41–45 %) of the cases no hemodynamic variable was used. Static markers of preload were used in 785 of 2213 cases (36 %, CI 34–37 %). Dynamic indices of preload responsiveness were used in 483 of 2213 cases (22 %, CI 20–24 %). No safety variable for the FC was used in 72 % (CI 70–74 %) of the cases. There was no statistically significant difference in the proportion of patients who received further fluids after the FC between those with a positive, with an uncertain or with a negatively judged response. *Conclusions:* The current practice and evaluation of FC in critically ill patients are highly variable. Prediction of fluid responsiveness is not used routinely, safety limits are rarely used, and information from previous failed FCs is not always taken into account.

Introduction

Many liters of intravenous fluids are used per year to treat critically ill patients worldwide. Fluids are one of the most commonly used therapies in critically ill patients and represent the cornerstone of hemodynamic management in intensive care units (ICUs) [1]. The basic physiological target of administration of fluids is to improve tissue perfusion. Hemodynamic optimization with fluids has been shown to improve patient outcome when applied in the perioperative period and in the early phases of sepsis [1–4]. Timing of the intervention is important; in the context of shock, higher fluid administration in the first 3 h was associated with better outcome in a retrospective study [5]. On the other hand, liberal administration of fluids may lead to a positive fluid balance [6] which is independently associated with a poor outcome [7]. Accordingly, in patients with respiratory failure, once hemodynamically stable, fluid restriction is associated with earlier weaning from mechanical ventilation [8].

Altogether, it seems reasonable to give the needed amount of fluids when hemodynamically patients are unstable and to restrict fluids when they are stabilized. Such an approach makes physiological sense and in theory should bring better outcomes to the patients. Whereas in overt bleeding, fluids are often given without guidance with specific hemodynamic monitoring, in other conditions, when hypovolemia may be subtler or when the response to fluids is more variable, fluids may be given on the basis of monitoring their hemodynamic impact. This practice, the "fluid challenge" technique (FC) was proposed more than 30 years ago [9–11]. Over recent decades new techniques have been developed in order to monitor and predict the response to fluids. The roles of static markers of preload such as central venous pressure (CVP) and pulmonary artery occlusion pressure (PAOP) have been questioned and dynamic indices of preload have been studied [12–14]. The use of dynamic indices is now recommended [4] but many technical limitations may preclude their use.

However, no data exist on the manner in which FCs are indicated and performed in critically ill patients around the globe. We conducted a multicenter international observational study aiming to evaluate the indications, current practice, and judgment of benefit of FCs in critical care settings. We hypothesized that there is an extensive variation in the current practice of FC.

Methods

This was an observational study conducted by the ESICM Trials Group (17–23 April 2013 or 23–29 May 2013) and registered on ClinicalTrials.Gov (NCT01787071). ICUs were able to enter the study in one of the 2 weeks. The possibility to choose between 2 weeks was chosen in order to compensate for differences in national holidays in different countries and therefore to maximize the recruitment of study units. IRB approval was obtained in each country and the local investigators were responsible to ensure that with local and national requirements were fulfilled. In most participating countries informed consent from the patient was waived owing to the observational study design. National coordinators and local investigators are listed in the electronic supplementary material (ESM).

We included all consecutive adult (18 years old and above) patients, up to a maximum of 20 per participating unit, in whom an FC was performed during a 1-week period. FC was defined as administration of any bolus of fluid (crystalloid or colloid) in less than 2 h. Administration of red blood cells or fresh frozen plasma was not considered as

an FC. The exclusion criteria were previous inclusion in the study, overt bleeding, and time of an FC exceeding 120 min. Only one FC, ideally the first, was considered for each patient. Only one FC per patient was recorded.

We collected data on patient demographics, indications for the FC, the type, amount, and rate of fluids administered, available hemodynamic variables, and judgment on the efficacy and safety of the FC. The case report form (CRF) is available in the ESM. Anonymous CRF data were uploaded by local investigators using a Web-based electronic CRF (Clinfile, Sevres, France). The data were stored securely in a server located in Brussels. All procedures regarding data management complied with the EU directive on data protection (95/46/EC).

Study aims

The primary aim of this study was to evaluate how physicians indicate FC.

The secondary aims were

- to evaluate the type, volume, and rate of fluid administered during an FC.
- to evaluate variables used to trigger/indicate an FC, and to judge the effect or safety of an FC.
- to compare the proportion of patients receiving further fluid administration based on the response to the fluid challenge, as judged by the bedside clinician after a fluid challenge.

Statistical analysis

Categorical variables are described as numbers (percentages) and continuous variables as mean (±standard deviation), if normally distributed, or median [interquartile range] if not normally distributed. The paired *t* test or Wilcoxon test was used to compare hemodynamic variables after the FC with baseline, when applicable. Proportions of patients were compared with χ^2 test and data presented as proportions and odd ratios. A p value of less than 0.05 was considered statistically significant. We targeted a minimum of 100 study sites with a maximum of 20 FCs each and a minimum of 1000 patients.

Results

We included 2279 patients with an FC from 311 centers across 46 countries (ESM). Of those 2279, 66 patients were excluded from the analysis as a result of at least one exclusion criterion (see the study flow chart, Fig. 1 ESM). A total of 2213 patients were analyzed.

Data on demographic factors and concomitant treatment are presented in Table 1. The main diagnostic groups were sepsis ($n = 595$, 27.0 % [CI 25.2–28.9 %]), cardiac ($n = 454$, 20.6 % [CI 18.9–22.3 %]), and respiratory failure ($n = 238$, 10.8 % [CI 9.5–12.1 %]).

The median amount of fluid given during an FC was 500 ml [500–1000]. The median time was 24 min [40–60 min], and the median rate of fluid administration was 1000 [500–1333] ml/h. Crystalloids were the most used (in 74.0 % [CI 72.2–75.8 %] of the cases) including normal saline in 45.9 % [CI 25.2–28.9 %], and balanced solutions were used in 53.5 % [CI 51.4–55.6 %] of FCs (Table 2).

The main indication for fluid administration was hypotension in 1211 (58.7 % [CI 56.7–60.1 %]) of FCs. In 42.7 % [CI 40.6–44.8 %] of the cases no hemodynamic variable was used to predict fluid responsiveness. Static markers of preload were used in 785 of 2213 cases (35.5 % [CI 33.5–37.5 %]). In 572 of 785 of these cases (89.9 % [CI 87.8–92.0 %]) CVP was the leading variable used (25.8 % [CI 24.0–27.6 %] of all FCs). Dynamic indices of preload responsiveness were used in 483 of 2213 cases (21.9 % [CI 20.2–23.6 %]). In 238 of those 483 cases (49.3 % [CI 44.8–53.8 %]) passive leg raising (PLR) was the leading variable (10.7 % [CI 9.4–12.0 %] of all FCs) (Table 3).

The response to fluid administration was judged as positive in 1544 of 2213 (69.8 % [CI 67.9–71.7 %]) of the FCs, most often as an increase in arterial blood pressure (1039 of 1544, 67.3 % [CI 65.0–69.7 %]). No safety variable for the FC was used in 72.0 % [CI 70.1–73.9 %] of the cases. When used, CVP was the most common variable (57 %). Further fluids were administered in 1050 of 2213 (49.8 % [CI 47.7–51.9 %]) of the cases. The proportion of patients who received further fluids after was similar in patients with a positive (47.9 ± 2.5 %), with an uncertain [52.4 ± 7.1 %, OR 0.94 (0.76–1.16)] or with a negatively judged response to FC [49.4 ± 6.6 %, OR 0.83 (0.62–1.13)] ($p = 0.46$ by χ^2 test) (Fig. 1).

Discussion

The two major findings of this large global multicenter observational study comprising 2213 patients are first a significant variability in the conduction of FC and second the fact that the response to the initial FC does not have an impact when prescribing further fluid administration. These findings were observed in critically ill patients all around the world. All aspects of the FC, the type, volume, and rate of given fluids, and more importantly the indication, evaluation of possible benefit, and safety variables used varied significantly. It is possible that some of the

Table 1 Baseline characteristics and concomitant treatments in critically ill patients ($N = 2213$)

Age (years)	63 ± 16
Female sex	824 (37.3 [35.3–39.3])
Reason for admission to ICU [*n* (%)]	
Medical	962 (43.5 [41.4–45.6])
Surgical	691 (31.2 [29.3–33.1])
Emergency surgical	548 (24.8 [23.0–26.6])
Main diagnosis	
Sepsis	595 (27.0 [25.2–28.9])
Cardiac	454 (20.6 [18.9–22.3])
Respiratory	238 (10.8 [9.5–12.1])
Neurologic	180 (8.2 [7.1–9.3])
Trauma	141 (6.4 [5.4–7.4])
Intoxication	41 (1.9 [1.3–2.5])
Other	558 (25.3 [23.5–27.1])
SOFA score	7 [4–10]
Physiological variables	
HR (bpm)	95 ± 24
MAP (mmHg)	70 ± 16
CVP (mmHg)	8 ± 5
Urine output (ml/h)	40 [20–80]
Fluid balance previous 24 h (ml)	2698 [1500–3945]
Lactate (mmol/L)	1.8 [1.1–2.9]
Vasopressor/inotropic agents	
Dopamine (*n* (%); μg/kg min)	91 (4); 5 [4–10]
Norepinephrine (*n* (%); μg/kg min)	903 (41); 0.16 [0.07–0.34]
Epinephrine (*n* (%); μg/kg min)	74 (3); 0.1[0.03–0.30]
Dobutamine (*n* (%); μg/kg min)	159 (7); 4 [3–5]
Mechanical ventilation, *n* (%) of 2172	
None	736 (33.8 [31.8–35.8])
Noninvasive ventilation	64 (2.9 [2.2–3.6])
Invasive mechanical ventilation	1372 (63.1 [61.1–65.1])
Characteristics of patients under invasive mechanical ventilation	*n* (%) of 1372
Sedation present	927 (67.6 [65.1–70.1])
Spontaneous ventilation included	602 (43.8 [41.2–46.4])
Renal replacement therapy, *n* (%) of 2087	
None	1930 (92.5 [91.4–93.6])
Dialysis	58 (2.8 [2.1–3.5])
Hemofiltration	99 (4.7 [3.8–5.6])

Qualitative data are given as absolute number (percentage); quantitative data are given as median value [interquartile range]

HR heart rate, *MAP* mean arterial pressure, *CVP* central venous pressure, *CVVH* continuous veno-venous hemofiltration

variability may be explained by variables not collected in our study, such as unit policies and protocols.

While we recorded only one FC per patient, we also recorded the decision for further fluid administration post FC. When looking at the response to fluid administration, investigators found a positive response only in seven cases out of ten. However, further fluids were given in comparable proportions of patients despite the initial response. If an FC is used to look at a dynamic response and to decide whether further fluids may be administered safely, one would expect that further fluids should be administered only in patients with a positive initial response. In our study the response to the initial fluid challenge made no difference to the decision for further fluid administration. This behavior seems to be harmful and highlights a huge need for education.

This huge variability in the current practice regarding an FC may reflect the presence of controversies in current guidelines. In the Surviving Sepsis Guidelines fluids are recommended in the very early phase of hemodynamic resuscitation of patients with severe sepsis [15]. In this case a fluid bolus is considered as administration of fluids of 30 ml/kg. In high-risk surgical patients fluid challenges are often given in smaller amounts [11]. In the perioperative setting there are guidelines covering the administration of fluids recommending the use of fluids for stroke volume optimization [16]. While it is true that different conditions may require different techniques, our data show extensive variability even within the same clinical condition.

Simple clinical signs led to FC in more than 80 % patients (hypotension, 58.7 %; oliguria, 18 %; or weaning of vasopressors, 7.1 %). Of note, markers of inadequate tissue perfusion such as lactate or skin mottling were used as an indication for an FC only in less than 8 % of the cases. This seems paradoxical since fluids are mostly indicated to increase cardiac output [11, 17, 18] and tissue perfusion [19]. Moreover, some studies focused on microcirculation clearly showed that clinical signs cannot predict microcirculatory

Table 2 Fluid challenge ($N = 2213$) characteristics

Volume (ml), median [IQR]	500 [500–999]		
Rate (ml/h), median [IQR]	1000 [500–1333]		
Type of fluids	*n*	% Of category	% All fluids
Crystalloids	1713		74.3 [72.5–76.1]
NaCl 0.9 %	786	45.9 [43.5–48.3]	34.1 [32.1–36.1]
Balanced	916	53.5 [51.1–55.9]	39.8 [37.8–41.8]
G5 % DW	4	0.2 [0.0–0.4]	0.2 [0.0–0.4]
G5 % NaCl 0.45 %	7	0.4 [0.1–0.7]	0.3 [0.1–0.5]
Colloids	591		25.6 [23.8–27.4]
HES	249	42.1 [38.1–46.1]	10.8 [9.5–12.1]
Albumin 4–5 %	101	17.1 [14.1–20.1]	4.3 [3.5–5.2]
Gelatin	203	34.3 [30.5–38.1]	8.8 [7.6–10.0]
Dextran	13	2.2 [1.0–3.4]	0.5 [0.2–0.8]
Albumin 20 %	25	4.2 [2.6–5.8]	1.1 [0.7–1.5]

NaCl saline, *balanced* crystalloids with chloride concentration lower than saline (i.e., Plasma Lyte, Hartman's), *G5 %* glucose 5 %, *DW* dextrose in water, *HES* hydroxyethyl starch

Table 3 Indications and variables used to predict fluid responsiveness ($N = 2213$)

Indication			*n* (%)
Hypotension			1211 (58.7 [56.7–60.8])
Weaning vasopressor			146 (7.1 [6.0–8.2])
Cardiac output			62 (3.0) [2.3–3.7]
Oliguria			372 (18.0 [16.4–19.6])
Skin mottling			36 (1.7 [1.2–2.2])
Lactate			128 (6.2 [5.2–7.2])
$SvO_2/ScvO_2$			10 (0.5 [0.2–0.8])
SVV/PPV			37 (1.8 [1.3–2.4])
CVP/PAOP			60 (2.9 [2.2–3.6])
Hemodynamic variable used to predict fluid responsiveness	*n*	% Of category	% All
No variable used	945		42.7 [40.6–44.8]
Any variable used	1268		57.3 [55.2–59.4]
Static	785		35.5 [33.5–37.5]
CVP	572	89.9 [87.8–92.0]	25.8 [24.0–27.6]
PAOP	31	4.9 [3.4–6.4]	1.4 [0.9–1.9]
GEDVI	33	5.2 [3.6–6.8]	1.5 [1.0–2.0]
Other	149	23.4 [20.4–26.4]	6.7 [5.7–7.8]
Dynamic	483		21.9 [20.2–23.6]
PPV	88	18.2 [14.8–21.6]	4.0 [3.2–4.8]
SVV	88	18.2 [14.8–21.6]	4.0 [3.2–4.8]
PPV + SVV	24	5.0 [3.1–6.9]	1.1 [0.7–1.5]
PLR	238	49.3 [44.8–53.8]	10.7 [9.4–12.0]
Echo variables	45	9.3 [6.7–11.9]	2.0 [1.4–2.6]

SvO_2 mixed venous oxygen saturation, *$ScvO_2$* central venous oxygen saturation, *SVV* stroke volume variation, *PPV* pulse pressure variation, *CVP* central venous pressure, *PAOP* pulmonary artery occlusion pressure, *GEDVI* global end diastolic volume, *PLR* passive leg raising, *Echo* echocardiography

impairment [20] and that improving MAP and diuresis is not sufficient for improving patient outcome [21–23].

These findings are in line with the ones published by Boulain and coauthors [24]. In their study, limited to ICUs in France, low blood pressure and low urine output were the most used triggers for fluid administration. The wider scope of our study demonstrates that this is common practice around the globe. It is interesting that so much attention is paid to the blood pressure at the bedside. This variable is the most used both for triggering and assessing the response to an FC. It is possible that the goal of many clinicians is the one of increasing BP with an FC. On the other hand it is possible that arterial blood pressure was used as a surrogate of cardiac output (CO). This seems common practice despite the known limitations of this variable when used to estimate CO. The increase in arterial pressure during an FC for instance is variable and depends on vascular tone and arterial elastance [25]. In patients increasing their CO in response to fluids, arterial blood pressure increases only in those with high arterial elastance [26, 27]. In summary, while fluids are mostly indicated to increase cardiac output [11, 17, 18] and tissue

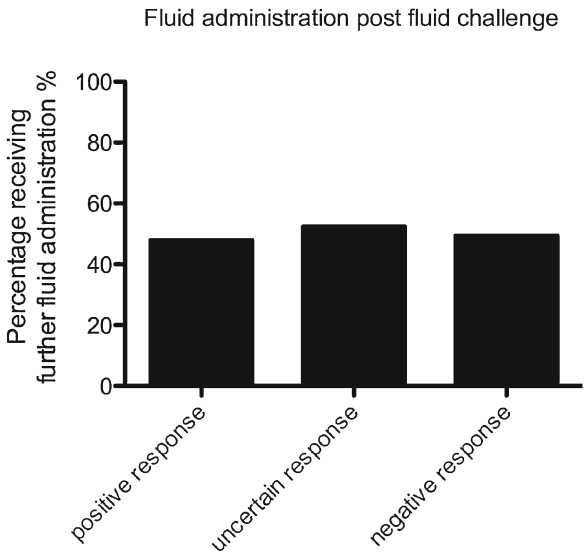

Fig. 1 Further fluid administration post fluid challenge

Further fluid administration – n (%)	1050 (47.4 ± 2.5)	
with an initial positive response n (%) OR	739 (47.9 ± 2.5)	Ref
with an initial negative response n (%) OR	212 (49.4 ± 6.6)	OR 0.94 (0.76-1.16)
with an initial uncertain response n (%) OR	99 (52.4 ± 7.1)	OR 0.83 (0.62-1.13)

perfusion [19] and not to just to increase blood pressure, at the bedside clinicians rely heavily on this variable both to predict and assess fluid responsiveness (Table 4).

Importantly, in almost half of the patients no hemodynamic variable was used to predict fluid responsiveness—and if used CVP was used most often. This is interesting considering that the CVP is a poor variable to predict fluid responsiveness [12, 14, 28].

The use of dynamic indices of preload was infrequent in our study. Cyclical changes in stroke volume (stroke volume variation, SVV) and pulse pressure (pulse pressure variation, PPV) during mechanical ventilation have been shown to predict fluid responsiveness with high sensitivity and specificity [29]. However, one of the limitations is that the patient has to be in controlled ventilation with tidal volumes equal to or higher than 8 ml/kg of ideal body weight [30], and with no arrhythmias. It is possible that the limited use of these three dynamic indices (in total 9 % of patients) was influenced by a high prevalence of patients with preserved spontaneous breathing activity. Another possible explanation is that we encouraged investigators to look at the first fluid challenge in our study. In this case flow monitors may have not have been in place yet. In this scenario though, we would have expected a more prevalent use of echocardiography. Of note, this was used to indicate FC in only 2 % of the patients.

Passive leg rising is a maneuver that produces an autologous fluid challenge by shifting venous blood from the legs to the intrathoracic compartment. The response measured by a flow monitor is able to predict the response to a fluid challenge. This has been studied and validated with different flow monitors. With a lower degree of accuracy with respect to cardiac output and stroke volume, blood pressure monitoring could be used for this technique, too [31]. Considering that an increase in blood pressure was used as the positive indicator of a fluid challenge in two-thirds of the cases, our data suggest that arterial pressure is the hemodynamic variable on which the majority of clinicians focus. Hypotension and weaning of vasopressor were the main indications to give an FC and the response in arterial pressure was the most used one for evaluation of possible benefit.

Our findings highlight a possible safety problem. Half of the patients with a negative response received further fluids. Of note, in three out four cases no safety limits were used at all. While CVP is a poor marker of preload and fluid responsiveness, it is one of the regulating functions of the venous return and a raise in CVP may be used as a safety limit [9, 32–34]. Given this finding and that patients received further fluids despite no response to the initial FC, the current practice and evaluation of FC and fluid administration in critically ill patients seems to be arbitrary, not evidence-based and possibly harmful.

We also found a high variability in the type of fluid used with higher use of crystalloids compared to colloids. It is difficult to interpret these results, since this study was performed during a time of high debate among intensive care clinicians following the publication of large

Table 4 Judged response to fluid challenge

Response classification [no. (%) of 2162]	
Negative response	429 (19.8 [18.1–21.5])
Positive response	1544 (71.4 [69.5–71.4])
Uncertain	189 (8.7 [7.5–9.9])
Variable use to evaluate response [no. (%) of 1544 with positive response]	
Increase in BP	1039 (67.3 [65.0–69.7])
Decrease vasopressors	56 (3.6 [2.7–4.5])
Increase in CO	174 (11.3 [9.7–12.9])
Increase in SV	100 (6.5 [5.3–7.7])
Decrease in HR	374 (24.2 [22.1–26.3])
Urine output	590 (38.2 [35.8–40.6])
Lactate	281 (18.2 [16.3–20.1])
Skin perfusion	128 (8.3 [6.9–9.7])
Mental state	40 (2.6 [1.8–3.4])
$ScvO_2/SvO_2$	77 (5.0 [3.9–6.1])
SVV/PPV	110 (7.1 [5.8–8.4])
CVP/PAOP	256 (16.6 [14.7–18.5])
Other	132 (8.5 [7.1–9.9])
Safety limit used [no. (%) of 2213]	577 (27.9 [25.7–30.1])
Variable used in the safety limit group [no. (%) of 577]	
CVP	329 (57.0 [53.0–61.0])
PAOP	39 (6.7 [4.7–8.8])
GEDVI	11 (1.9 [4.7–8.8])
EVLWI	28 (4.9 [3.1–6.7])
SpO_2/SaO_2	105 (18.2 [15.1–21.35])
CO	8 (1.4 [0.4–2.4])
SVV/PPV	80 (13.9 [11.1–16.7])
Other	120 (20.8 [17.5–24.1])

BP blood pressure, *CO* cardiac output, *SV* stroke volume, *HR* heart rate, SvO_2 mixed venous oxygen saturation, $ScvO_2$ central venous oxygen saturation, *SVV* stroke volume variation, *PPV* pulse pressure variation, *CVP* central venous pressure, *PAOP* pulmonary artery occlusion pressure, *GEDVI* global end diastolic volume, *EVLWI* extravascular lung water index

randomized controlled trials advocating the use of crystalloids versus colloids [1, 35–38].

Our study has some obvious strengths. First, to the best of our knowledge this study is the largest prospective observational study investigating FCs in critically ill patients and thus provides a reasonably exact estimate of the current practice of the FCs given. Second, the international multicenter design limiting the cases from individual sites increases its external validity. However, there are several limitations of our study to be considered. First, we recorded only when FCs were given and not when FCs were not given. Thus, in practice we may have underestimated the times when variables used to predict fluid responsiveness were used. Second, we encouraged investigators to record data on the first fluid challenge, which may have several implications. At early stages, a positive response to fluids is more likely and patients are often less invasively monitored. Studying patients at later stages may have yielded different results. Third, we allowed a wide range of options (volume, type of fluid, first or subsequent FC) to be recorded during an FC. It is possible that some investigators considered an FC what would be normally defined a more sustained volume expansion.

We conclude that the current practice and evaluation of FC in critically ill patients seems to be arbitrary. While not demonstrable in this observational study, this practice does not seem evidence-based and could be harmful.

Our findings highlight an urgent need for more educational activities and more research to assess whether a more standardized approach to a fluid challenge could lead to better patient-centered outcomes.

Conflicts of interest Antonio Artigas is a scientific advisor of B. Braun and Ferrer, received a restricted research grant from Grifols and Pulsion, and is an invited speaker of Grifols. Michael Sander received financial support from Masimo, Pulsion, Edwards Lifesciences, and Maquet. Jean-Louis Teboul is a member of the medical advisory board of Pulsion. The other authors declare no conflict of interest.

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